



Treating AIDS-associated cerebral toxoplasmosis – pyrimethamine plus sulfadiazine compared with co-trimoxazole, and outcome with adjunctive glucocorticoids

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We conducted a retrospective study of AIDS-associated cerebral toxoplasmosis. Eighteen patients received pyrimethamine plus sulfadiazine and 25 co-trimoxazole, with comparable baseline characteristics. There were no differences in clinical outcomes,

but co-trimoxazole was better tolerated ($p = 0.066$). There was also a trend towards more deaths among patients who received glucocorticoids.

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The current standard treatment for AIDS-associated cerebral toxoplasmosis is pyrimethamine plus sulfadiazine (PS). PS has been associated with high toxicity rates.^{1,2} Several alternative therapies, principally used in patients intolerant to sulfonamides, have been reported to be effective: clindamycin plus pyrimethamine,³ clarithromycin plus pyrimethamine,⁴ and atovaquone.⁵ Folinic acid must be co-administered with pyrimethamine to prevent bone marrow suppression. Co-trimoxazole (trimethoprim plus sulfamethoxazole) (TMP-SMX) had a similar efficacy to PS for treating AIDS-associated cerebral toxoplasmosis and was better tolerated in a retrospective study,¹ followed by a randomised controlled trial conducted by the same group.⁶ TMP-SMX is more affordable than the other anti-toxoplasmosis therapies, particularly as co-administration with folinic acid is not required. There are limited published data on the use of TMP-SMX in cerebral toxoplasmosis in sub-Saharan Africa, where efficacy and adverse events may be different from those reported in other populations. A study examined the efficacy of TMP-SMX in 20 South African AIDS patients with cerebral toxoplasmosis, but it had no comparator arm and non-responders were excluded from the analysis.⁷

In our centre the treatment policy for AIDS-associated cerebral toxoplasmosis was changed from PS to TMP-SMX after the withdrawal of sulfadiazine from the South African market. In this retrospective study we compared the clinical outcomes and tolerability of PS and TMP-SMX. Although glucocorticoids are often added as adjuvant therapy in clinical practice, a retrospective study concluded that neither

beneficial nor harmful effects could be attributed to their use.² We therefore also examined the role of glucocorticoids in the management of toxoplasmosis.

Patients and methods

We reviewed the records of all HIV-infected adult patients with a diagnosis of cerebral toxoplasmosis at discharge. They had been admitted to Groote Schuur Hospital, a teaching hospital affiliated to the University of Cape Town, between 1992 and 2003. Patients were identified from an electronic database of hospital discharge diagnoses. Sulfadiazine has been unavailable in South Africa since 1999. Patients treated from 1992 to 1998 received PS, while those treated during 1999 - 2003 received TMP-SMX. The following diagnostic criteria were used for cerebral toxoplasmosis: multiple intracranial mass lesions (demonstrated on either MRI or CT scan), or a single lesion supported by positive toxoplasmosis serology, or a single lesion with an improvement in clinical or radiological parameters in response to treatment.

Patients were stratified on entry according to the British Medical Research Council criteria as modified by Thwaites *et al.*:⁸ grade I Glasgow Coma Scale (GCS) of 15 with no focal neurological signs; grade II GCS of 11 - 14, or 15 with focal neurological signs; and grade III GCS of 10 or less. Clinical outcomes at discharge were considered only for the first admission for toxoplasmosis. Outcomes were categorised as complete recovery, disability or death. Disability was defined as persistent neurological sequelae, mental handicap or uncontrolled seizures at discharge.

Stata 8.0 was used to describe and compare baseline characteristics and outcomes in the treatment groups, using Fisher's exact test for categorical data and the Kruskal-Wallis test for continuous data. The study was approved by the Research Ethics Committee of the University of Cape Town.

Results

Of the 58 patients treated for presumed cerebral toxoplasmosis between 1992 and 2003, 43 fulfilled our diagnostic criteria for

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the condition. Table I summarises the baseline characteristics, clinical outcomes and adverse events by antimicrobial treatment. The baseline characteristics were similar for both groups, except for a slight age difference, which is unlikely to be clinically significant. There was no difference in the clinical outcomes between the treatment groups at discharge. There was a trend towards more frequent renal impairment after treatment with PS than with TMP-SMX (3/18 v. 0/25; $p = 0.066$). Twenty-six patients received adjunctive glucocorticoids (Table II). There were no significant differences in the level of consciousness ($p = 0.139$) and CD4 count ($p = 0.43$) of those who received glucocorticoids compared with those who did not, but there was a trend towards an increased risk of death among patients who received glucocorticoids (6/26 v. 0/17; $p = 0.066$).

Discussion

In our study it was found that there was no difference between TMP-SMX and PS in terms of the clinical outcomes of full recovery, disability and death. There was a trend towards more frequent renal impairment in the PS group. Haematological toxicity was not significantly different between the two groups, probably because we routinely prescribed folic acid for all patients on PS. These findings are in keeping with the results of a randomised controlled trial ($N = 77$) of TMP-SMX compared with PS for AIDS-associated cerebral toxoplasmosis, which concluded that there was no difference in clinical efficacy

between the two treatments, and that TMP-SMX was better tolerated.⁶

Cerebral toxoplasmosis is generally treated empirically in AIDS patients with compatible neuro-imaging studies and positive serology. A South African study demonstrated on biopsy or aspiration that toxoplasmosis was the commonest cause of intracranial mass lesions in HIV-infected adults.⁹ Therefore we are confident that subjects fulfilling our inclusion criteria almost certainly had cerebral toxoplasmosis.

Clinicians prescribe adjunctive glucocorticoids for cerebral oedema frequently surrounding intracranial mass lesions of toxoplasmosis. These drugs were prescribed to 60% of patients in our study. However, there is no evidence that adjunctive glucocorticoids improve outcome. They can be potentially harmful and can mask alternative diagnoses. This is particularly important given that the diagnosis of cerebral toxoplasmosis is generally made in response to empiric therapy. Alternative diagnoses in AIDS patients include tuberculomas, cryptococcomas and lymphomas – all of which may improve transiently with glucocorticoids if surrounding cerebral oedema is present.

In our study the trend towards more deaths in the glucocorticoid group is of concern, as these drugs appear to be widely used. Patients in the glucocorticoid group were comparable with those who did not receive glucocorticoids with regard to their neurological baseline characteristics and CD4 counts. Until the role and safety of glucocorticoids in

Table I. Baseline characteristics and treatment response in 43 HIV patients with cerebral toxoplasmosis by antimicrobial treatment group

| | Pyrimethamine-sulfadiazine ($N = 18$) | Co-trimoxazole ($N = 25$) | p |
|--|--|--------------------------------|-------|
| Demographics | | | |
| Median age (IQR) | 34 (32 - 41) | 31 (27 - 34) | 0.025 |
| Male | 9 (50%) | 9 (36%) | 0.359 |
| Clinical parameters | | | |
| Level of consciousness | | | |
| Grade I | 3 (17%) | 2 (8%) | 0.634 |
| Grade II | 15 (83%) | 23 (92%) | 0.634 |
| Seizures | 10 (56%) | 17 (68%) | 0.405 |
| Concurrent tuberculosis | 4 (22%) | 5 (20%) | 1.000 |
| Laboratory parameters | | | |
| Median CD4 count ($10^6/l$) (IQR) ($N = 23$) | 43 (8 - 77) | 14 (4 - 25) | 0.226 |
| Median haemoglobin (g/dl) (IQR) ($N = 41$) | 11 (8.8 - 13.7) | 10.4 (9.4 - 11.7) | 0.560 |
| Positive toxoplasmosis serology ($N = 27$) | 12/13 (92%) | 14/14 (100%) | 0.290 |
| Outcome | | | |
| Full recovery | 7 (39%) | 11 (44%) | 0.738 |
| Disability | 9 (50%) | 10 (40%) | 0.736 |
| Death | 2 (11%) | 4 (16%) | 1.000 |
| Adverse events | | | |
| Renal dysfunction | 3 (17%) | 0 (0%) | 0.066 |
| Liver impairment | 2 (11%) | 0 (0%) | 0.169 |
| Total | 4 (22%) | 1 (4%) | 0.144 |

IQR = interquartile range.

**Table II. Baseline characteristics and treatment response in 43 HIV patients with cerebral toxoplasmosis by adjuvant glucocorticoid treatment group**

| | Adjunctive glucocorticoids | | p |
|--|----------------------------|-----------------|-------|
| | Yes (N = 26) | No (N = 17) | |
| Demographics | | | |
| Median age (IQR) | 32 (27 - 37) | 34 (31 - 35) | 0.129 |
| Male | 11 (42%) | 7 (44%) | 0.941 |
| Clinical parameters | | | |
| Level of consciousness | | | |
| Grade I | 5 (19%) | 0 (0%) | 0.139 |
| Grade II | 21 (81%) | 17 (100%) | 0.139 |
| Seizures | 18 (69%) | 9 (53%) | 0.280 |
| Concurrent tuberculosis | 4 (24%) | 5 (19%) | 1.000 |
| Laboratory parameters | | | |
| Median CD4 count (10 ⁶ /l) (IQR) (N = 23) | 14 (4 - 38) | 25.5 (8 - 75) | 0.403 |
| Median haemoglobin (g/dl) (IQR) (N = 41) | 10.1 (9 - 11.55) | 11 (9.1 - 13.7) | 0.218 |
| Positive toxoplasmosis serology (N = 27) | 14/14 (100%) | 12/13 (92%) | 0.481 |
| By treatment group | | | |
| TMP-SMX | 18 (69%) | 7 (41%) | 0.068 |
| Outcome | | | |
| Full recovery | 10 (39%) | 8 (47%) | 0.576 |
| Disability | 10 (39%) | 9 (53%) | 0.350 |
| Death | 6 (30%) | 0 (0%) | 0.066 |

IQR= interquartile range.

the management of cerebral toxoplasmosis are clarified in a controlled trial, we would advocate using them only for toxoplasmosis patients with life-threatening compression caused by oedema surrounding intracranial mass lesions.

Our study has important limitations. The small sample size limits our power and the retrospective design does not allow for control of all confounders.

Authors' roles: NC and GM conceived and designed the study; JA drafted the paper; JA, KB and GM analysed and interpreted the data; and NC, KB and GM revised it critically for intellectual content.

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